(19) JAPANESE PATENT OFFICE (JP) (12) **OFFICIAL GAZETTE FOR PATENT APPLICATIONS** (A) (11) Unexamined Patent Application Publication Disclosure (Kokai) No.: **7-89875**

(43) Disclosure Date: April 4,1995

(51) Int. Cl.[6]		ID Code(s)	Intra-Bureau Nos.	FI	Basis classification
A 61 K	47/26	Z			
	9/20	E			
	31/435	ACB	9454-4C		

Request for Examination: Not filed. Number of Claims: 6 OL (Total of 9 pages)

(21) Application No.: No. 5-232684

(22) Filing Date: September 20, 1993

(71) Applicant: 000002831
Dai'ichi Seiyaku Co.
3-14-10 Nihonbashi, Chuo-ku, Tokyo-to

(72) Inventor: Takahiro Matsumoto
c/o Dai'ichi Seiyaku Co., Tokyo Research Center
1-16-13 Kitakasai, Edogawa-ku, Tokyo-to

(72) Inventor: Katsuhiko Nagao
c/o Dai'ichi Seiyaku Co.
1-10-7 Hacchobori, Chuo-ku, Tokyo-to
Matsuda Yaesudori Bldg., 5th Floor

(54) [Title of the Invention] Tablet With No Delay in Disintegration

(57) [Abstract]

[Object] To prevent delays in the disintegration time of tablets containing polyethylene glycol and hydrophobic lubricants, and to prevent delayed elution in the disintegration of drugs.

[Structure To provide a tablet comprising a sucrose fatty acid ester, polyethylene glycol, lubricant, and drug.

[Effect] The above tablet prevents delays in disintegration time and delays in the elution of drugs from the tablet under stringent hot storage conditions or hot and humid storage conditions, while preserving good tabletability and quality.

[Claims]

[Claim 1] A tablet with no delay in disintegration, comprising

(a) a sucrose fatty acid ester,

(b) lubricant,

(c) binder, and

(d) drug having physiological activity.

[Claim 2] A tablet with no delay in disintegration according to Claim 1, wherein the HLB of the sucrose fatty acid ester of ingredient (a) ranges from 3 to 7.

[Claim 3] A tablet with no delay in disintegration according to Claim 1 or 2, wherein the lubricant of ingredient (b) is one or a mixture of two or more selected from magnesium stearate, calcium stearate, hydrogenated oil, stearic acid, and aluminum stearate.

[Claim 4] A tablet with no delay in disintegration according to any of Claims 1 through 3, wherein the binder of ingredient (c) is one or a mixture of two or more selected from polyethylene glycol 4000, polyethylene glycol 6000, and polyethylene glycol 20,000.

[Claim 5] A tablet with no delay in disintegration according to any of Claims 1 through 5 [sic], wherein the sucrose fatty acid ester of ingredient (a) is a sucrose stearic acid ester, sucrose palmitic acid ester, or mixture thereof.

[Claim 6] A tablet with no delay in disintegration according to any of Claims 1 through 5, wherein the drug having physiological activity of ingredient (d) is (S)-(2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)) acetic acid ester or salt thereof.

[Detailed Description of the Invention]

[0001]

[Field of Industrial Utilization] The invention relates to a drug product tablet.

[0002]

[Prior Art] Conventional methods commonly used to manufacture tablets include methods in which a lubricant is mixed with a powder, and the mixture is then tableted, and methods in which a powder is granulated to produce a granular material of suitable granularity, which is then mixed with a lubricant and then tableted.

[0003] When producing tablets that contain active ingredients that are unstable in moisture, dry granulation, which does not involve the addition of water, is used for producing tableting granules in the preliminary stages of tablet production instead of wet granulation, which does involve the addition of water during the granulation process.

[0004] Primary dry granulation methods include common dry milling (method A) and melt granulation (method B). Dry milling (method A) is a method in which a binder such as polyethylene glycol is added to the active ingredient and an excipient to produce plate-shaped solids which are then milled to produce granulated material. Melt granulation (method B) is a method in which a low boiling substance such as polyethylene glycol is melted to join the active ingredient and excipient, forming a granulated material (Japanese Unexamined Patent Application (Kokai) 58-214333; Japanese Examined Patent Application (Kokoku) 4-13019).

[0005] Granulated material produced by either Method A or B above is mixed with a suitable amount of a lubricant such as magnesium stearate to prevent tableting malfunctions, and the mixture is then tableted into tablets. Because the resulting tablets are sometimes stored for long periods of time or under hot and humid conditions, or because of the heat when coated with a film, they may sometimes fail to disintegrate, or may take a long time to do so, after administration or in solution.

[0006]

[Problems Which the Invention Is Intended to Solve] An object of the invention is to provide a tablet which is obtained by dry granulation after the addition of a lubricant, yet suffers no delays in disintegration after administration or in solution.

[0007]

[Means for Solving Problems] As a result of extensive research to overcome such drawbacks, the inventors were able to provide a tablet with no delays in disintegration (tablets in which delays in disintegration are prevented) upon the discovery that blending a sucrose fatty acid ester with tablets made it possible to dramatically curtail delays in disintegration time caused by hot and humid conditions or the heat during film coating. The tablet of the invention with no delays in disintegration refers to tablets in which delays in disintegration time caused by heat treatment or the moisture absorbed during storage are prevented.

[0008] The present invention relates to a tablet with no delays in disintegration as described in (1) through (6) below.

(1) A tablet with no delay in disintegration, comprising (a) a sucrose fatty acid ester, (b) lubricant, (c) binder, and (d) drug having physiological activity.

(2) A tablet with no delay in disintegration according to any of (1) through (4), wherein the HLB of the sucrose fatty acid ester of ingredient (a) ranges from 3 to 7.

(3) A tablet with no delay in disintegration according to (1) or (2), wherein the lubricant contained in the tablet of the invention is one or a mixture of two or more selected from magnesium stearate, calcium stearate, hydrogenated oil, stearic acid, and aluminum stearate.

(4) A tablet with no delay in disintegration according to any of (1) through (3), wherein the binder contained in the table of the invention is one or a mixture of two or more selected from polyethylene glycol 4000, polyethylene glycol 6000, and polyethylene glycol 20,000.

(5) A tablet with no delay in disintegration according to any of (1) through (4), wherein the sucrose fatty acid ester contained in the tablet of the invention is a sucrose

stearic acid ester, sucrose palmitic acid ester, or mixture thereof.

(6) A tablet with no delay in disintegration according to any of (1) through (5), wherein the drug having physiological activity contained in the tablet of the invention is (S)-(2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)) acetic acid ester or salt thereof.

[0009] The various ingredients of the tablet of the invention are described below. The sucrose fatty acid ester contained in the tablet of the invention is one in which sucrose acid is bound by an ester to a fatty acid. The physical and chemical properties of sucrose fatty acid esters are naturally affected by the type and number of fatty acids bound per sucrose fatty acid molecule.

[0010] In the interests of tabletability, sucrose fatty acid esters which can be used in the tablet of the invention must be in the form of solids at ambient temperature. The criteria for determining if a sucrose fatty acid ester can be used in the invention can be based on the HLB (hydrophile-lipophile balance), which is a physicochemical property of sucrose fatty acid esters. The HLB of sucrose fatty acid esters which can be used in the invention is in the range of 0 to 15, and preferably 3 to 7.

[0011] In view of the above, the most typical examples of the sucrose fatty acid ester of ingredient (a) include sucrose stearic acid esters and sucrose palmitic acid esters. Sucrose behenic acid esters and sucrose lauric acid esters are also included. In addition to the various sucrose fatty acid esters contained as principal ingredients, there are mixtures of other esters (other than the main esters) and free ones. Examples of esters include monoesters, diesters, triesters, and mixtures thereof. Accordingly, other esters mean diesters and triesters when the principal ester is a monoester, and monoesters and triesters when the principal ester is a diester. Similarly, other esters mean mono-esters and diesters when the principal ester is a tri-ester.

[0012] In the case of sucrose stearic acid esters, for example, the others can be those other than monoesters of sucrose and stearic acid, such as stearic acid diesters and triesters, and free ones (sucrose alone or stearic acid alone). In most cases, the mixtures will be of varying proportions. The agent for preventing delayed disintegration in the invention includes any one, or mixtures, of such esters. Similarly, in the case of sucrose palmitic acid esters, the others can be those other than sucrose palmitic acid monoesters, such as diesters and triesters, and free ones (sucrose alone or palmitic acid alone). In most cases, the mixtures will be of varying proportions. The agent for preventing delayed disintegration in the invention includes any one, or mixtures, of such esters.

[0013] Even though mixtures of sucrose fatty acid esters other than the one that is the principal component are included, if the HLB is 0 to 15, and preferably 3 to 7, they can be used as the sucrose fatty acid ester serving as the agent for preventing delayed disintegration in the invention. The content of the sucrose fatty acid ester that is used will depend on the granularity and properties of the resulting granular material, but from the standpoint of tabletability and moisture absorption, the content should range between 0.5% and 10% per part powder.

[0014] Examples of the lubricant included in the tablet of the invention include higher fatty acid metal salts, fatty acids, hydrogenated oils, and the like. Examples of metal salts of higher fatty acids include magnesium stearate, calcium stearate, and aluminum stearate. A typical example of a fatty acid is stearic acid. The lubricant content can be 0.5 to 5%. The lubricant is added to prevent friction with the mortar or pestle and sticking during tableting.

[0015] The binder, which is another ingredient of the agent for preventing delays in disintegration in the invention is described below. Polyethylene glycol with an average molecular weight of 600 to 20,000 can be used because it is a solid at ambient temperature, but those with an average molecular weight of 4000 to 20,000 are preferred because of the need for a melting point of 53 to 64°C. Typical examples are polyethylene glycol 4000, 6000, and 20,000. These may be used individually or in combination. The amount in which the polyethylene glycol is added can be adjusted according to the type of the separately added excipient and active ingredient, the amount of the active ingredient, and the intended granularity of the granular material. Specifically, 2 to 40% can be added, and 5 to 25% is preferred.

[0016] Drugs having physiological activity which can be added as ingredient (d) in the agent of the invention are described below. The drug in the invention can be any drug with physiological activity that is administered to humans or animals. The drug is not particularly limited by the intended application, and can be a drug having any effect. Anti-platelet agents are an example of such a drug having physiological activity as ingredient (d) in the invention. An example of an anti-platelet agent is Clopidogrel hydrogen sulfate ((S)-(2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c] pyridin-5-yl)) acetic acid ester or salt thereof). This compound is a suitable drug for the agent of the

invention and can be blended with excellent effect in preventing delayed disintegration.

[0017] Tablets can be prepared by directly tableting a powder or by granulating the powder before it is tableted. Granulating methods for the latter method are divided into wet and dry methods. Dry granulation includes common milling and melt granulation. The method for producing an agent that prevents delayed disintegration in the invention is characterized by being particularly useful in cases where the drug is unstable in water because the method is based on dry granulation. The content of the drug having physiological action as ingredient (d) in the invention can be 1 to 90%, and is preferably 5 to 50%.

[0018] Other excipients, disintegrants, and the like can be included in addition to the essential ingredients (a) through (d) in the agent of the invention. These are described below. Examples of excipients which can be used include lactose, corn starch, and crystalline cellulose. The content of such excipients must be adjusted according to the content of the active ingredient and physicochemical properties such as the intended dissolution rate of the active ingredient in the tablet. The content can be 5 to 95%, and preferably 50 to 90%, among the tablet ingredients.

[0019] Disintegrants can be included in the other ingredients in the agent of the invention. Examples of such disintegrants include carmelose (hydroxypropyl cellulose), carmelose calcium, cross carmelose sodium, and derivatives thereof. The content can be adjusted as needed, ranging from 5 to 20%.

[0020] Methods for producing the agent for preventing delayed disintegration in the invention are described below. As noted above, methods for producing the agent of the invention include dry granulation (method A) and melt granulation (method B), which will be each described. In Method A, a suitable amount of an excipient such as corn starch and a suitable amount of a solid binder are mixed to homogeneity with the active ingredient in a suitable mixer, the resulting powder mixture is molded or tableted using a dry granulator, the molded material is then milled using a suitable mill, and it is sifted, giving a granulated material. The use of polyethylene glycol as the binder is preferred in such cases. A slag tableter or roller compactor can be used, for example, as the dry granulator.

[0021] In melt granulation (method B), a suitable amount of active ingredient, a suitable amount of an have a granularity befitting the intended granularity are excipient, and a suitable amount of a solid binder that introduced into a suitable granulator such as a fluidized bed granulator or stirred granulator, the contents are stirred or fluidized while heated, and the powder components are allowed to adhere to the binder during the melt step. Granulated material is then obtained by cooling the material to below the melting point of the polyethylene glycol. Suitable amounts of the above ingredients (active ingredient, excipient, binder) can be used after pretreatment such as milling.

[0022] The granulated material obtained by either dry granulation (method A) or melt granulation (method B) is sifted, and is then mixed with lubricant and sucrose fatty acid ester using a mixer. A V-shaped mixer or the like can be used as the mixer. The granulated mixture is then tableted by a tableter, yielding tablets. A one-shot tableter, rotary tableter, or the like can be used.

[0023]

[Effect of the Invention] The agent for preventing delayed disintegration in the present invention produced in the manner described above will markedly improve delays in the elution of the drug because the addition of the sucrose fatty acid ester will prevent or control delays in the disintegration of tablets under stringent hot storage or hot and humid storage conditions.

[0024] The invention is illustrated by, but is not limited to, the following examples.

[Example 1] 4000 g lactose (by DMV), 250 g corn starch (by Nippon Shokuhin Kogyo), 500 g of polyethylene glycol 6000 (P type, by Nippon Fats & Oils), and 300 g low substituted hydroxypropyl methyl cellulose (by Shin-Etsu Kagaku Kogyo) were introduced into a fluidized bed dry granulator (Grad WSG-5), and the contents were heated while fluidized to the set air intake temperature of 90°C, melting the polyethylene glycol 6000. The powder ingredients adhered to the polyethylene glycol 6000 during the melting process, and when it was confirmed that there was no loose powder in the fluidized bed, cool air was allowed to flow in, cooling the polyethylene glycol 6000 to below the melting point to give a granulated product. The resulting granules were sifted using a 16-mesh sieve, and 50 g magnesium stearate and 50 g sucrose fatty acid ester (S-370, by Mitsubishi Kasei Shokuhin) were mixed for 10 minutes in a V-shaped mixer. The resulting granules for tableting were tableted using a rotary tableter (by Hata Seisakusho, HT-15A), yielding tablets 8 mm in diameter.

[0025]

[Example 1 Formulation]

Lactose	4000 g
Corn starch	250 g
Polyethylene glycol 6000(*)	500 g
Low substituted hydroxypropyl methyl cellulose	300 g

Magnesium stearate	50 g
Sucrose fatty acid ester(**)	50 g

*: P type, by Nippon Fats & Oils

**: S-370, by Mitsubishi Kasei Shokuhin

[0026] [Comparative Example 1] Tablets were obtained in the same manner as in Example 1 except that the sucrose fatty acid ester of the Example 1 formulation was left out.

[Comparative Example 1 Formulation]

Lactose	4000 g
Corn starch	250 g
Polyethylene glycol 6000	500 g
Low substituted hydroxypropyl methyl cellulose	300 g
Magnesium stearate	50 g

[0027] [Test Example 1] Tablets from Example 1 and Comparative Example 1 were stored at 60°C and at 40°C and 75% relative humidity (RH), and the various disintegrating times were determined. The disintegration times were determined using water as sample solution based on the disintegration tests in the 12th Revised Japan Pharmacopoeia. That is, 6 tablets were tested to determine the disintegration time of each tablet. The disintegration times given in Table 1 are the minimum and maximum times determined from six tablets.

[0028] [Table 1]

Table 1: Disintegration times of tablets from Example 1 and Comparative Example 1

Storage conditions	Disintegration time (min)	
	Example 1	Comp. Example 1
1. Initial	10 to 20 min	10 to 20 min
2. 7 days at 60°C	15 to 25 min	50 to 60 min
3. 14 days at 60°C	20 to 30 min	50 to 60 min
4. 1 month 40°C 75% RH	20 to 30 min	40 to 50 min
5. 3 months 40°C 75% RH	20 to 30 min	45 to 55 min

(Note): 75% RH is 75% relative humidity

[0029] The results showed that the addition of the sucrose fatty acid ester resulted in obviously better disintegration (Table 1).

[0030] [Example 2] Tablets were obtained in the same manner as in Example 1 except for the use of 50 g hydrogenated oil instead of the 50 g magnesium stearate in the Example 1 formulation.

[Example 2 Formulation]

Lactose	4000 g
Corn starch	250 g
Polyethylene glycol 6000	500 g
Low substituted hydroxypropyl methyl cellulose	300 g
Hydrogenated oil	50 g
Sucrose fatty acid ester	50 g

[0031] [Comparative Example 2] Tablets were obtained in the same manner as in Example 2 using [sic] the sucrose fatty acid ester of the Example 2 formulation.

[Comparative Example 2 Formulation]

Lactose	4000 g

Corn starch	250 g
Polyethylene glycol 6000	500 g
Low substituted hydroxypropyl methyl cellulose	300 g
Hydrogenated oil	50 g

[0032] The tablets of Example 2 and Comparative Example 2 were stored at 60°C and at 40°C and 75% relative humidity (RH) to compare the disintegration times.

[0033] [Test Example 2]

The disintegration times of tablets from Example 2 and Comparative Example 2 were determined using water as sample solution based on the disintegration tests in the 12th Revised Japan Pharmacopoeia. The tablets containing the sucrose fatty acid ester of Example 2 showed obviously better disintegration.

[0034]

[Table 2]

Table 2: Disintegration times of tablets from Example 2 and Comparative Example 2

Storage conditions	Disintegration time (min)	
	Example 2	Comp. Example 2
1. Initial	10 to 20 min	10 to 20 min
2. 7 days at 60°C	20 to 30 min	50 to 60 min
3. 14 days at 60°C	20 to 35 min	60 min or more
4. 1 month 40°C 75% RH	20 to 30 min	40 to 50 min
5. 3 months 40°C 75% RH	30 to 40 min	40 to 55 min

(Note): 75% RH is 75% relative humidity

[0035] [Example 3]

130 g lactose, 7 g corn starch, and 8 g polyethylene glycol 6000 (P type, Nippon Fats & Oils) were mixed for 5 minutes in a plastic bag and then introduced into a mini-roller compactor (Freund Co.), the contents were then passed through a 1 mm screen, milled, and granulated, giving granules. Crystalline cellulose, 5 g magnesium stearate, and 5 g sucrose fatty acid ester were then mixed with the resulting granules for 10 minutes in a plastic bag. The resulting tableting granules were tableted from a one-shot tableter (Okada Seiko), giving tablets 8 mm in diameter.

[0036] [Example 3 Formulation]

Lactose	130 g
Corn starch	7 g
Polyethylene glycol 6000	8 g
Crystalline cellulose	10 g
Magnesium stearate	5 g
Sucrose fatty acid ester	5 g

[0037] [Comparative Example 3] Tablets were obtained in the same manner as in Example 3 using [sic] 5 g sucrose fatty acid ester of the Example 3 formulation.

[Comparative Example 3 Formulation]

Lactose	130 g
Corn starch	7 g
Polyethylene glycol 6000	8 g
Crystalline cellulose	10 g
Magnesium stearate	5 g

[0038] [Test Example 3]

The tablets of Example 3 and Comparative Example 3 were stored at 60°C and at 40°C and 75% relative humidity (RH) to compare the disintegration times. The disintegration times of tablets from Example 3 and Comparative Example 3 were determined using water as sample solution based on the disintegration tests in the 12th Revised Japan Pharmacopoeia.

[0039]

[Table 3]

Table 3: Disintegration times of tablets from Example 3 and Comparative Example 3

Storage conditions	Disintegration time (min)	
	Example 3	Comp. Example 3
1. Initial	10 to 15 min	10 to 15 min
2. 7 days at 60°C	10 to 15 min	30 to 40 min
3. 14 days at 60°C	10 to 20 min	30 to 40 min
4. 1 month 40°C 75% RH	10 to 20 min	25 to 35 min
5. 3 months 40°C 75% RH	10 to 20 min	30 to 40 min

(Note): 75% RH is 75% relative humidity

[0040] The results showed that the addition of the sucrose fatty acid ester resulted in obviously better disintegration (Table 3).

[0041] [Example 4]

Tablets were obtained in the same manner as in Example 3 except for the use of 5 g hydrogenated oil instead of the 5 g magnesium stearate in the Example 3 formulation.

[Example 4 Formulation]

Lactose	130 g
Corn starch	7 g
Polyethylene glycol 6000	8 g
Crystalline cellulose	10 g
Hydrogenated oil	5 g
Sucrose fatty acid ester	5 g

[0042] [Comparative Example 4]

Tablets were obtained in the same manner as in Example 3 without the 5 g sucrose fatty acid ester of the Example 4 formulation.

[Comparative Example 4 Formulation]

Lactose	130 g
Corn starch	7 g
Polyethylene glycol 6000	8 g
Crystalline cellulose	10 g
Magnesium stearate	5 g

[0043] [Test Example 4]

The tablets of Example 4 and Comparative Example 4 were stored at 60°C and at 40°C and 75% relative humidity (RH) to compare the disintegration times. The disintegration times of tablets from Example 4 and Comparative Example 4 were determined using water as sample solution based on the disintegration tests in the 12th Revised Japan Pharmacopoeia.

[0044]

[Table 4]

Table 4: Disintegration times of tablets from Example 4 and Comparative Example 4

Storage conditions	Disintegration time (min)	
	Example 4	Comp. Example 4
1. Initial	10 to 15 min	10 to 15 min
2. 7 days at 60°C	15 to 20 min	20 to 30 min
3. 14 days at 60°C	15 to 20 min	30 to 40 min
4. 1 month 40°C 75% RH	15 to 25 min	20 to 30 min
5. 3 months 40°C 75% RH	15 to 25 min	25 to 35 min

(Note): 75% RH is 75% relative humidity

[0045] The results showed that the addition of the sucrose fatty acid ester resulted in obviously better disintegration (Table 4).

[0046] [Example 5]

2284 g active ingredient, 2168 g lactose, 245 g partially gelatinized starch, 525 g polyethylene glycol 6000, and 300 g crystalline cellulose were introduced into a fluidized bed granulator, the air intake temperature was set to 90°C, and the contents were fluidized while heated, melting the polyethylene glycol 6000. The powder ingredients adhered to the polyethylene glycol 6000 during the melting process, and when it was confirmed that there was no loose powder in the fluidized bed, cool air was allowed to flow in, cooling the polyethylene glycol 6000 to below the melting point to give a granulated product. The resulting granules were sifted using a 16-mesh sieve, and 80 g hydrogenated oil and 50 g sucrose fatty acid ester were mixed for 10 minutes in a V-shaped mixer. The resulting granules for tableting were tableted using a rotary tableter (by Hata Seisakusho, HT-15A), yielding tablets 6 mm in diameter.

[0047] [Example 5 Formulation]

Drug (active ingredient)	2284 g
Lactose	2168 g
Partially gelatinized starch	245 g
Polyethylene glycol 6000	525 g
Crystalline cellulose	300 g
Hydrogenated oil	80 g
Sucrose fatty acid ester	50 g

[0048] [Comparative Example 5]

Tablets were obtained in the same manner as in Example 1 [sic] except that the sucrose fatty acid ester of the Example 5 formulation was left out.

[Comparative Example 5 Formulation]

drug (active ingredient)	2284 g
lactose	2168 g
partially gelatinized starch	245 g
polyethylene glycol 6000	525 g
crystalline cellulose	300 g
hydrogenated oil	80 g

[0049] Tablets from Example 4 [sic] and Comparative Example 4 [sic] were stored at 60°C and at 40°C and 75% relative humidity (RH), and the various disintegrating times were determined.

[0050] [Test Example 5]

The disintegration times of tablets from Example 4 [sic] and Comparative Example 5 were determined using water as sample solution based on the disintegration tests in the 12th Revised Japan Pharmacopoeia. The results showed that the addition of the sucrose fatty acid ester resulted in obviously better disintegration (Table 5).

[0051]

[Table 5]

Table 5: Disintegration times of tablets from Example 5 and Comparative Example 5

Storage conditions	Disintegration time (min)	
	Example 5	Comp. Example 5
1. Initial	10 to 20 min	10 to 20 min
2. 7 days at 60°C	20 to 30 min	50 to 60 min
3. 14 days at 60°C	20 to 30 min	50 to 60 min

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Corporate Translations, Inc.
77 Hartland St. | East Hartford, CT 06108
Tel: 860-727-6000 | Fax: 860-727-6001
www.corptransinc.com

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Authorized Signature:

Mary C. Gawlicki

Mary Gawlicki
President
Corporate Translations, Inc.

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